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Appendix 1

Spiration research group: Cedars-Sinai Medical Center, Los Angeles, Calif: R. McKenna, W. Houck, D. Kusuanco; Cleveland Clinic Foundation, Cleveland, Ohio: A. Mehta, T. Gildea, S. Murthy, Y. Meli; North Shore University Hospital–Long Island Jewish Health System, Manhasset, NY: D. Ost, A. Talwar, E. Figueredo; University of Pennsylvania Medical Center, Philadelphia, Pa: D. Sterman, A. Musani, M. Machuzak, A. Haas, B. Finkel; University of Washington Medical Center, Seattle, Wash: D. Wood, M. Mulligan, K. Seymour.

Data Safety Monitoring Board: Gordon Snider (Chairman), Bartolome Celli, Jamie Stoller, and Satoshi Furukawa.

Clinical Events Committee: Roger D. Yusen (Chairman), Matthew Brenner, and Stephen D. Cassivi.

Discussion

Dr John D. Mitchell *(Denver, Colo)*. Doug, I want to congratulate you and your coinvestigators on this very nice study, article, and presentation. Two of the biggest problems with surgical LVRS are the attendant morbidity and mortality associated with the procedure and the cost. One would hope that the development of less-invasive endobronchial therapies, such as this valve, could lead to expansion of the subgroup of patients with emphysema who might benefit from LVRS with less risk and at a lesser cost.

I just have a couple of questions for you. First, I wonder whether you could comment on some of the technical aspects of valve implantation. Is general anesthesia necessary? Are some segments and subsegments harder to instrument than others? And is this what led to considerable variation or range of the procedure times seen in the study?

Dr Wood. In terms of the first part of that question, general anesthetic is probably not necessary. We chose to use general anesthesia in this initial experience to decrease the possible technical difficulties and variability of doing this in an awake patient. All that said, I think that even later, as we gain experience, there still might be some benefit of doing it with a general anesthetic. There is a lot of airway manipulation of multiple segments, and it is very easy to do with a patient anesthetized. I think that the aspect of cough or respiratory movement might make some of those adjustments and placement of the valve more difficult. I do not have experience with that yet, but I can anticipate that that might be the case.

In terms of segments that are more difficult: yes, there are. As you get more acute angles into the anterior segments of both upper lobes, those can sometimes be difficult angles to achieve. Fortunately, the fact that we have a delivery catheter that goes through the flexible bronchoscope and can be visualized going into that segment does make it easier and that has become easier, for example, in the last 8 patients, as I describe. Still, sometimes the angles are difficult in the anterior segments.

Does that relate to the variability in procedure time? Possibly. I am not sure. I think that obviously this is an initial experience, and therefore the investigators as they were first doing this were completely new to the procedure, so that this involves all of the learning curve of doing the procedure as well, which I think we have gotten better at, but I think we would have to have substantially more experience to know whether we can decrease that time reliably.

Dr Mitchell. Second, were you surprised at the relative lack of complications caused by the valves? Specifically, I am interested in either valve migration or postobstructive pneumonia.

Could you comment on the hyperplastic tissue response that was seen associated with some of the valves several months after implantation?

Dr Wood. That is a good question. I am somewhat surprised. I expected first of all an instance of pneumothorax, which has been seen in similar trials of the Emphasis valve. They have had a significant incidence of pneumothorax, which we did not have in this initial phase A of our pilot trial, but I would have expected a big concern in plugging the airways of a patient with COPD as opposed to obstructive pneumonia. The valve is obviously purposely designed to allow mucus secretions to pass proximal to the valve, yet still it is functionally obstructed, and I would expect an instance of postobstructive pneumonia distal to these valves that, fortunately, we did not see. With additional time, we might.

In terms of the hyperplastic tissue, I have now removed valves in 2 of my patients out 1 year because they have not had a substantial improvement and now wanted to be considered for LVRS, and we wanted to remove the valves before that. They have had variable amounts of hyperplastic tissue obscuring the valves. Fortunately, we still have been able to remove all valves—100% of the ones that I have done even at 12 months—but some of them do have hyperplastic tissue proximal to the valve.

Dr Mitchell. Third, you were able to report that a substantial number of patients had a meaningful change in their health-related quality of life comparable with that seen in the NETT. When you did that comparison, did you use patients in the NETT with similar anatomic findings to those in your study?

Dr Wood. No, and it is not really possible to do that because that requires access to the primary data, which are not yet released for the NETT, to be able to try to stratify it to that degree. Therefore this is just a general NETT population.

Dr Mitchell. Finally, as I mentioned before, it would be nice if the use of these less-invasive technologies could expand the pool of patients with emphysema eligible for LVRS. In this study you limited your patient population to those who met generally the NETT criteria and had upper lobe–predominant disease, perhaps the group that you would expect to have the best outcome from this procedure. Could you comment or maybe speculate how this device might work in those with non–upper lobe disease, those deemed high risk by NETT criteria, perhaps even those with homogeneous disease and those with significant medical comorbidities?

Thank you very much. I enjoyed the article.

Dr Wood. Thank you, John. In terms of speculation and the reason for selecting this most favorable subset as an initial pilot series, you can probably understand the desire to do that when your initial study is a safety study looking at feasibility more than effectiveness. That is the reason for the stringent selection criteria in this phase. You are right that if in this phase it proves to be effective and a pivotal trial, then I think we should expand the indications and look at patients who otherwise might have contraindications to LVRS, as I introduced at the beginning of this, who might benefit from this or other forms of endobronchial therapy.

Dr Jerome McDonald *(Lakewood, Wash)*. One of my concerns about this particular procedure over LVRS is that you have developed an obligate shunt, and I was wondering whether there is going to be any assessment in your future trials of efficacy with any perfusion studies or any way to assess whether an obligate shunt is going to decrease some of the effectiveness or efficacy of the procedure.

Dr Wood. In fact, most likely what has happened is the opposite of what you are talking about, which is an improvement in ventilation-perfusion match rather than a worsening. In fact, if you look at these patients, they have such low compliance in their upper lung fields that they are preferentially ventilated but very poorly perfused. Therefore, in fact, one of the ways that valves might be effective in improving patient quality of life is actually by improving ventilation-perfusion mismatch by decreasing the ventilation in an area that is already underperfused.

Dr Donald Low *(Seattle, Wash)*. Doug, I enjoyed the article. I would specifically like to ask you a question regarding something that is in your abstract regarding follow-up bronchoscopy. It looks like that was a routine aspect of your ongoing assessment in these patients. I would like you to just let us know when this was done, and interestingly, I note that 17 patients—more than half of your patients—either had valve revision or additional valves placed. The valve revision issue is interesting considering how low your migration or other problems were. Could you tell us a little bit about what that valve revision was all about and what indicated the need for additional valves in selected patients on the follow-up bronchoscopy?

Dr Wood. Very astute of you, Don. I actually left that out because of lack of time, but in fact the protocol required a 1-month follow-up bronchoscopy that we wanted to do to assess valve placement and adequacy of seating of each of the valves and lack of migration, so that was a part of the planned protocol. All patients had a follow-up bronchoscopy at 1 month. Of the 30 patients, 17 of them had some revisions of their valves at that 1-month planned bronchoscopy. Some of them had valves removed. Some of them had valves removed and replaced, and some had additional valves placed. The most common rationale for each of them was not any valve migration but an appearance of a valve that looked like it might not be occlusive because of angulation or because of a wrinkle in the valve membrane that we thought could possibly be improved by a different size or better seating of the valves, and therefore those valves were removed and replaced. That was the most common indication. The reason for new valves being placed is sometimes that we were cautious in the initial placement and did not necessarily occlude every segment that we would like to and with more confidence would treat additional segments at the second bronchoscopy. Actually, after the second bronchoscopy, there were 10 more valves than the 184 that I presented in the article here.

Dr Henning Gaissert *(Boston, Mass)*. I very much enjoyed your presentation, Doug. In other areas of the airway, when prosthetic devices are being placed, it is not necessarily clinical infection but colonization with particular organisms that indicate a higher risk of long-term infection, these organisms being particularly *Staphylococcus aureus* and *Pseudomonas* species. Have you done any culturing of the airway to see whether you get these specific organisms?

Dr Wood. No, we have not.

Dr Gaissert. Thank you. I very much enjoyed it.

Unidentified speaker. Nicely done, Doug. As to volume reduction surgery, one of the ways it works is it reduces the size of the lungs and mechanics improve and so on. Do you have any idea whether you are actually reducing the size of these lungs with these valves? Do you see it?

Dr Wood. The answer to that is, at least in this pilot experience with the first 30 patients, no. We are not reducing the size of the lungs, and that is kind of what my next-to-last slide was about. We have different mechanisms working here than mechanisms that we thought were going to be working when we try to duplicate LVRS. Clearly the patients are having an improvement in quality of life, but the objective measures that we have used in LVRS are not necessarily representing the reason that these patients are having an improvement. It might be things like dynamic hyperinflation. I will say just as a teaser that we have moved into a second phase of this study already and with a slightly different valve design and some more aggressive treatment, and in that group we are starting to see volume reduction as well with the atelectasis that we would kind of like to see. Surgically what we were thinking that we were aiming for is an atelectasis developing in the upper lobes to mimic the effects of LVRS, but at least in these first 30 patients, that was not seen to any reliable degree.

Dr Joseph Shrager *(Philadelphia, Pa)*. Doug, how is it that these did not have surgical LVRS? In other words, did they have to be assessed by a surgeon or decline having surgical LVRS, given that you have a proved therapy and now have an experimental therapy?

Dr Wood. It is a good question. Some of these patients were not candidates for LVRS. For example, one of my patients had a previous coronary artery bypass graft and was not a candidate for LVRS but would very much be a candidate for an endobronchial therapy. Other patients were candidates for either, and they were all in centers that could do LVRS, obviously in surgical centers like ours. They were all counseled about the choices of LVRS or involvement in this clinical trial. At the other centers, with the pulmonary physicians as principal investigators, there was the same counseling. The effort was to provide patients with counseling about all of their options, including surgical volume reduction.

Dr Shrager. The other issue is, can you speculate about why—you touched on this a little bit—the FEV_1 is not improved, whereas the quality of life is improved?

Dr Wood. Well, the FEV_1 surprisingly was not improved where quality of life was and that is where I think our dilemma is, except we know that FEV_1 is not a reliable surrogate for improvement after LVRS either, with a substantial number of patients having much more significant improvement in their functional capacity and quality of life that is not well represented by FEV_1. Our problem is that we are not yet very good at measuring the right measurement, and FEV_1 is common, so we use it a lot, but it is not a very reliable measure of efficacy in these types of treatments for emphysema.

GTS